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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/819,094	03/27/2001	Richard I. Weiner	UCSF-018/02US	6968

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EXAMINER	
BRANNOCK, MICHAEL T	
ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 11/26/2002 14

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/819,094	Weiner et al.
Examiner	**Art Unit**
Michael Brannock	1646

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Sep 16, 2002*.

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-5 and 27-30* is/are pending in the application.

4a) Of the above, claim(s) *4, 5, 29, and 30* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-3, 27, and 28* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☒ The drawing(s) filed on *Mar 27, 2001* is/are a) ☒ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 8
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Status of Application: Claims and Amendments

1. Applicant is notified that the amendments put forth in Paper 13, 9/16/02 have been entered in full.

2. Claims 1-5 and new claims 27-30 are pending.

3. Claims 4, 5, 29 and 30 withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species of invention, there being no allowable generic or linking claim. Applicant is reminded that generic claims 1, 2, and 27 will be examined only to the extent that they read on the elected species of human Placental Lactogen peptide. As no arguments have been presented as to why the species election might be improper, the election is treated as being made without traverse in Paper No. 13.

Oath/Declaration

4. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

- Non-initialed and/or non-dated alterations have been made to the oath or declaration, e.g. the correction of Frauke Bentzien's address has not been initialed and dated. See 37 CFR 1.52(c).

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claim 28 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. New claim 28 requires that the polypeptide be in a pharmaceutically acceptable carrier at a concentration range of about 0.8 to 1 nM; At page 6, line 9, the specification indicates that the IA_{50} of the peptides is approximately 0.8-1 nM, however the specification says nothing indicating that the peptides be present in a pharmaceutically acceptable carrier at these concentrations, and neither could such be reasonably inferred.

7. Claims 1, 2, and 27 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an anti-angiogenesis peptide consisting of approximately 135 N-terminal residues of human Placental Lactogen, does not reasonably provide enablement for a genus of anti-angiogenic peptides substantially identical to about 10-150 consecutive amino acids of human Placental Lactogen. The specification does not

enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The specification indicates that a polypeptide corresponding to the 16 kD fragment of placental lactogen (-1 Met - 134 Arg), has the property of inhibiting angiogenesis (e.g. page 54, yet the claims require a vast genus of fragments of this peptide. The specification has provided no guidance as to which of these claimed fragments would be expected to work. Further, the skilled artisan would expect that the majority of such fragments would not work as claimed. Khurana et al. Endocrinology 140(9)4127-4132, 1999 teach that peptides of the 16 kDa fragment of Prolactin missing the first 53 amino terminal residues lacked anti-angiogenesis activity, see for example the middle paragraph of the first column of page 4131. The close structural and functional relationship between human Placental Lactogen and Prolactin is well recognized, as reviewed by Corbacho et al., J. Endocrinology 173(219-238)2002 see page 229, col 2 for example; thus one skilled in the art would expect similar results with Placental Lactogen. Further, the relationship between structure and function among Prolactin-like family members is known to be complex and not well understood (see page 220: middle paragraph of col 1 and the first paragraph of col 2). The specification has not provided guidance as to any correlation between the structure of the fragments and the desired function of the fragments, such that the skilled artisan could make a structure and expect a function. The specification has failed to provide adequate guidance as to which of the multitude of fragments claimed might have the desired activity. Thus, the skilled artisan is required to embark on an extensive plan of research,

wherein the claimed fragments are made and tested in a random, trial and error, fashion to try to find fragments that meet the limitations of the claim.

Therefore, due to the large quantity of experimentation necessary to generate the tremendous multitude of peptide fragments recited in the claims and screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the requirement for a significant portion of the N-terminus of Prolactin for activity, and the breadth of the claims which require as few as 10 residues for activity, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 1, 2 and 27 are rejected under 35 U.S.C. 102(b) as being anticipated by U.S. Patent No: 4189426, to Choh, 2/1980.

Choh disclose the proteolytic N-terminal fragment of human Placental lactogen, a.k.a. human choriomammotropin (HCS), see col 6. consisting residues 1-133, see col 7. Although Choh is silent with respect to the instantly claimed functional properties of the polypeptide, such would be expected to be inherent properties of the claimed product, absent evidence to the contrary. Further, the Choh disclose that the polypeptide be admixed in a pharmaceutically acceptable carrier, e.g. for use the rat tibia assay (see col 9).

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claim 3 is rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No: 4189426, as applied to claim 1 above in view of US Patent 4853332, to Mark et al., 8/1989.

Claim 3 requires the anti-angiogenic fragment of claim 1 having the amino acid sequence of SEQ ID NO: 18. As indicated above, Choh disclose the proteolytic N-terminal fragment of human Placental lactogen, and, absent evidence to the contrary, such a fragment would inherently possess the ability to inhibit angiogenesis. The polypeptide of SEQ ID NO: 18, however, has

been mutated to replace the reactive cysteine at position 53 and with serine. The reactive cysteine at this position is well known to be involved in a disulfide bond (e.g. see col 7, line 32 of Choh). Choh teaches that this reactive cysteine be neutralized by rendering it incapable of disulfide bond formation by any means known in the art (see col 1, last paragraph to col. 2). Consequently, Choh accomplish this by carboxamidomethylation, e.g. col 2 first paragraph. Subsequently, however, Mark et al. disclose an improved method of preventing undesirable disulfide formation at cysteine residues in peptide hormones, e.g. by mutagenically replacing the reactive cysteine residue with a non reactive residue (see col 1), e.g. with serine (e.g. col 5 line 23).

Therefore, it would be obvious to one of ordinary skill in the art at the time the invention was made, with reasonable expectation of success, to replace the cysteine residue at position 53 of the 16 kDa fragment of human placental lactogen, as taught by Choh, with a serine residue as taught by Mark et al.. The motivation to do so is provided by both Choh, who teaches that the reactive 53-cysteine be prevented from bond formation, and by Mark et al. who disclose an improved method to accomplish this in peptide hormones (e.g cols 1 and 2).

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Brannock, Ph.D., whose telephone number is (703) 306-5876. The examiner can normally be reached on Mondays through Thursdays from 8:00 a.m. to 5:30 p.m. The examiner can also normally be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, Ph.D., can be reached at (703) 308-6564.

Official papers filed by fax should be directed to (703) 308-4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

MB

November 22, 2002

YVONNE EYLER, PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600